
Differential effects of RUNX2 on the androgen receptor in prostate cancer: synergistic stimulation of a gene set exemplified by SNAI2 and subsequent invasiveness.

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Public Summary:

Targeting the AR–RUNX2 interaction presents an opportunity for the development of novel therapeutic approaches that would retain expression of androgen-stimulated tumor suppressors while preventing synergistic interaction between AR and RUNX2 at prostate cancer-driving genes. Such novel therapeutic approaches would be particularly suited to prevent disease recurrence in patients whose primary tumor biopsies exhibit high expression of AR, RUNX2, and SNAI2.

Scientific Abstract:

Changes to androgen signaling during prostate carcinogenesis are associated with both inhibition of cellular differentiation and promotion of malignant phenotypes. The androgen receptor (AR)-binding transcription factor RUNX2 has been linked to prostate cancer progression but the underlying mechanisms have not been fully defined. In this study, we investigated the genome-wide influence of RUNX2 on androgen-induced gene expression and AR DNA binding in prostate cancer cells. RUNX2 inhibited the androgen response partly by promoting the dissociation of AR from its target genes such as the tumor suppressor NKX3-1. However, AR activity persists in the presence of RUNX2 at other AR target genes, some of which are cooperatively stimulated by androgen and RUNX2 signaling. These genes are associated with putative enhancers co-occupied by AR and RUNX2. One such gene, the invasion-promoting Snail family transcription factor SNAI2, was co-activated by AR and RUNX2. Indeed, these two transcription factors together, but neither alone stimulated prostate cancer cell invasiveness, which could be abolished by SNAI2 silencing. Furthermore, an immunohistochemical analysis of SNAI2 in archived primary prostate cancer specimens revealed a correlation with the RUNX2 histoscore, and simultaneous strong staining for SNAI2, RUNX2, and AR (but not any pair alone) was associated with disease recurrence. Overall, our findings suggest cooperation between AR and RUNX in the stimulation of oncogenes such as SNAI2, which might be targeted for individualized prostate cancer therapy.

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